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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,185	STERN ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1,2,14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *3-13 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This office action is response to Applicant's election of Group III, claims 3-6, part of claims 7-9, claim 10, part of claims 11-13 and part of claims 16-25. Applicants have also elected autoimmune diseases as the species to be examined. Election was made with traverse in Paper No. 11 (3/27/03). The traversal is on the ground(s) that the search of all claims would not impose a serious burden on the Office. The elected invention is generic with respect to the species elected. Accordingly, the requirements for species election and applicants arguments are moot. This is not found to be persuasive because the three groups though treating inflammation in a subject by administering different compounds such as sRAGE, v-domain of RAGE and an agent that inhibits the interaction between RAGE and its ligand. Thus the mechanisms involved in the action are different. In addition, the search for a single compound will not automatically lead to the identification other compounds for the administration.. Therefore, the searches for each of the compounds are not coextensive and would be a burden on the office to search all of the inhibitors. Therefore, the restriction requirement is deemed proper and made FINAL.

Specification

2.The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Objections

3. Claims 7, 9, 11-13 and 16-25 are objected to because they recite multiple inventions (including those non-elected). Applicant is required to amend the claims to recite only the elected invention.

Drawings

4. The drawings have been objected to by the draftsperson (see attached 948). Appropriate correction is required.

Claim Rejections - 35 USC § 112

5.The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claim 5 is rejected as broad for reciting the term "a portion thereof" because the term "a portion thereof" is not defined in the specification. Therefore, the metes and bounds of these claims are unclear. This is because it is unclear what portion of a polypeptide is encompassed in this claim.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. Claims 3, 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses that the administration of soluble RAGE (sRAGE),or anti-RAGE or anti –EN-RAGE $F(ab')_2$ fragments markedly attenuated inflammation (see page 68, 1st paragraph). The specification also describes the amino acid corresponding to amino acid numbers 1-30 of the V-domain of sRAGE as an inhibitor (page 19, 2nd paragraph). This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible agents or portion thereof of AGE or portion thereof of RAGE or portion thereof of sRAGE contemplated by the Applicant. The claims as written, however, encompass agents and portions of polypeptide which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 3, 4 and 5. The specification does not provide written description to support the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of soluble RAGE (sRAGE),or anti-RAGE or anti –EN-RAGE $F(ab')_2$ fragments and amino acid corresponding to amino acid numbers 1-30 of the V-domain of sRAGE, the skilled artisan cannot envision all the detailed chemical structure or the mechanism of the claimed agents or portions of the polypeptide or the wide variety of molecules regardless of the complexity or simplicity of the method of identifying the agents or molecules. Applicant has failed to set forth any defining characteristics of the agents or molecules. No common structural or functional features essential for the claimed function are described, nor are a representative number of members of the claimed genus of inhibitory molecules presented.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated soluble RAGE (sRAGE),or anti-RAGE or anti –EN-RAGE $F(ab')_2$ fragments and amino acid corresponding to amino acid numbers 1-30 of the V-domain of sRAGE, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various agents and polypeptide sequences set forth in claims 3, 4 and 5.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

6b. Claims 3, 4, 5 and 16-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for administration of soluble RAGE (sRAGE),or anti-RAGE or anti –EN-RAGE $F(ab')_2$ fragments markedly attenuated inflammation (see page 68, 1st paragraph) and amino acid corresponding to amino acid numbers 1-30 of the V-domain of sRAGE (page 19, 2nd paragraph), does not reasonably provide enablement for all possible agents and portions of polypeptide contemplated by the Applicant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the

existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claim 3 recites "a method for treating inflammation in a subject which comprises administration to the subject an agent in an amount which inhibits the interaction between receptor for advanced glycation end product (RAGE) and its ligand...". The specification only describes the interaction of between RAGE and AGE (page 29, lines 28-30). In addition, the specification also describes the interaction of EN-RAGE (or Extracellular Novel RAGE-binding protein), which interacts with RAGE on cells (page 68, lines 1-4). Thus, the instant specification is only enabling for the binding of RAGE to either AGE or EN-RAGE and not "all" possible ligands that bind to RAGE. In the instant application, the quantity of experimentation needed to determine the limitless number of ligands that would interact with RAGE, is practically infinite and the guidance provided in the specification is very limited. Absent further guidance from the specification it would constitute undue experimentation to determine all the ligands that care capable of binding to the RAGE.

Furthermore, claim 3 recites "a method for treating inflammation in a subject which comprises administration to the subject an agent in an amount which inhibits the interaction between receptor for advanced glycation end product (RAGE) and its ligand...", and claims 4 and 5 recite "...wherein the agent comprises a polypeptide, a peptidomimetic, an organic molecule, a carbohydrate, a lipid, an antibody or a nucleic acid and wherein the polypeptide comprises an AGE polypeptide or a portion thereof, a RAGE polypeptide or a portion thereof, a sRAGE polypeptide or a portion thereof.."

respectively. The specification describes the use of sRAGE in treating wound healing in a diabetic mouse (Example 1, page 43), suppressing accelerated periodontal disease (Example 2, page 53), delayed hypersensitivity (Example 3, page 67), collagen-induced arthritis (Example 4, page 84) and experimental autoimmune encephalitis (Example 5, page 109). In addition, it also teaches the use of anti-RAGE antibody or anti-RAGE $F(ab')_2$ fragment or anti- ENRAGE $F(ab')_2$ fragment for the purpose inhibiting the interaction between receptor for advanced glycation end product (RAGE) and its ligand to treat inflammation. Thus, the instant specification is only enabling for a method of inhibiting inflammation in a subject by administering soluble RAGE (sRAGE),or anti-RAGE or anti –EN-RAGE $F(ab')_2$ fragments markedly attenuated inflammation (see page 68, 1st paragraph) and amino acid corresponding to amino acid numbers 1-30 of the V-domain of sRAGE (page 19, 2nd paragraph), and does not provide enablement for a method of inhibiting inflammation in a subject by administering "all" the claimed agents or portions of the polypeptide or the wide variety of molecules. In the instant application, the quantity of experimentation needed to determine the limitlessly possible agents or portions of the polypeptide or the wide variety of molecules that would inhibit the interaction between RAGE and its ligand, is practically infinite and the guidance provided in the specification is very limited. In addition, the instant claims are not limited to naturally–occurring compounds and the instant specification does not provide examples of representative compounds the interfere with the interaction of RAGE and its ligand. Absent further guidance from the specification it would constitute undue experimentation to determine all the claimed agents or portions of the polypeptide or the

wide variety of molecules the might inhibit with the interaction of RAGE and its ligand. As such, claims 3, 4 and 5 are not commensurate in scope with the specification but rather are broader that the supporting disclosure.

With respect to claims 19-25, which recite ".. wherein the subject is suffering asthma and diabetes", the instant specification is non-enabling for a method of treatment for any of the recited diseases, and is only enabling for a method of treatment of delayed-type hypersensitivity, collagen-induced arthritis, rheumatoid arthritis and periodontal disease (see examples 1-5). The instant specification provides no disclosure that inhibiting the interaction between RAGE and its ligand will indeed treat the subject for the various recited diseases including for example, colitis, asthma and diabetes because no nexus has been established that these diseases are caused by the interaction between RAGE and its ligand. Absent further guidance it would constitute undue experimentation to determine if all the recited diseases are induced by the interaction between RAGE and its ligand, and if so, in inhibiting this interaction would inhibit these diseases. Claims 6-13 are rejected insofar as they depend on claim 3 for the limitations set forth directly above in this paragraph.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 3-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morser et al. (U. S. Patent No: 5, 864,018) in view of Ritthaler et al. (1995).

The instant invention is directed to a method of treating inflammation in a subject by inhibiting the interaction between RAGE and its ligand.

Morser et al. disclose and teach that blocking agents inhibit or otherwise reduce the AGE/RAGE interaction (abstract). The reference teaches a soluble human RAGE (sRAGE) and antibodies to RAGE that inhibit the ability of ligands (such as AGEs and amphoterin) to bind to RAGE, said sRAGE or antibodies being useful for disorders or symptoms which result from the association between RAGE and its ligands (column 6, lines 53-56 and column 11, lines 53-56). Morser et al. also disclose methods of treatment for pathological conditions involving RAGE by administering orally, intravenously, intraperitoneal or intramuscularly, liposome formulations an effective amount of the sRAGe polypeptide or anti-RAGE antibodies to a mammal including humans (column 19 line 5 to column 20 line 28). However, Morser et al. reference does

not teach treatment of inflammation by administering an agent to inhibit the interaction between RAGE and its ligand.

Ritthaler et al. disclose that the interaction of AGE and RAGE may contribute to the developmet of vacular lesions and that examination of human atherosclerotis plaques or experimentally induced inflammatory lesions in response to local instillation of AGEs, showed prominent accumulation of cells strikingly positive for RAGE (see abstract and page 688, column 2), thus clearly implicating RAGE/AGE in inflammation related pathogenesis.

Therefore, it would have been *prima facie* obvious at the time of the invention to treat inflammation in a subject by inhibiting the interaction of AGE and RAGE by administering the sRAGE or the anti-RAGE antibodies disclosed by Morser et al., because Morser reference demonstrates that sRAGE or the anti-RAGE antibodies block the interaction between RAGE and its ligands, and Ritthaler et al. teach that RAGE and its ligands are involved in the diseases involving inflammation. With respect to claims 9-11, which recite the route of delivery and dosage respectively, it would have obvious to one of skill in the art to optimize the route of delivery and dosage of administering the sRAGE and anti-RAGE antibodies disclosed by Morser et al., to maximize the benefit for each subject. One of ordinary skill in the art would have been motivated to adapt the method of treating inflammation by inhibiting the interaction of RAGE and its ligands by administering sRAGE or the anti-RAGE antibodies described in Morser et al. and because Ritthaler et al. have showed that RAGE and its ligands may plat a role in

inflammation. Therefore, the instant invention is obvious over Morser et al. (U. S. Patent No: 5, 864,018) in view of Ritthaler et al. (1995).

7b. Claims 12, 13 and 16-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morser et al. (U. S. Patent No: 5, 864,018) Ritthaler et al. (1995) in view of Baker et al. (U. S. Patent No: 5, 998, 408)

The instant invention is directed to a method of treating inflammation associated with an autoimmune disease in a subject by inhibiting the interaction between RAGE and its ligand.

The relevance of Morser et al. and Ritthaler et al. has been set forth above in paragraph 7a. However, Morser et al. and Ritthaler et al. do not explicitly recite that the inflammation is associated with autoimmune disease. Baker et al. disclose autoimmune disease and inflammation associated with it (column 1) In addition, it also teaches discloses disease which are often involved inflammation or inflammatory process (columns 2-4).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to treat inflammation associated with auto immune disease by inhibiting the interaction of RAGE and its ligands by administering sRAGE or the anti-RAGE antibodies described in Morser et al. and because Ritthaler et al. have showed that RAGE and its ligands may plat a role in inflammation, with a reasonable expectation of success, because Baker et al discloses diseases involving inflammation, specifically the autoimmune process. Therefore, the claims are obvious over Morser et

al. (U. S. Patent No: 5, 864,018) Ritthaler et al. (1995) in view of Baker et al. (U. S. Patent No: 5, 998, 408)

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 3-11 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 47, 50, 55-60, 62-65 and 67 of copending Application No. 09/167705 in view of Morser et al. (U. S. Patent No: 5, 864,018) and of Ritthaler et al. (1995).

The teaching of Morser et al. and Ritthaler et al have been described above in 7a. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to treat inflammation by inhibiting RAGE interaction to its ligands by using an anti-EN-RAGE antibody or fragment thereof and the V-domain of soluble RAGE polypeptide or fragment because the inhibition of RAGE and its ligand binding and its role in inflammation has been described above. Therefore the instant

claims are obvios over claim 47 and 50 of copending Application No. 09/167705 in view of Morser et al. (U. S. Patent No: 5, 864,018) and of Ritthaler et al. (1995).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary L. Kunz

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JS
June 16, 2003